STATE MEDICAID P&T COMMITTEE MEETING

FRIDAY, November 16, 2007
7:00 a.m. to 8:30 a.m.
Cannon Health Building
Room 114

MINUTES

Committee Members Present:

Kort DeLost, R.Ph.
David Harris, M.D.
Koby Taylor, PharmD.
Howard Weeks, M.D.
Karen Gunning, PharmD.
Duane Parke, R.Ph.
Raymond Ward, M.D.
Jerome Wohleb, PharmD.

Board Members Excused:

Dept. of Health/Div. of Health Care Financing Staff Present:

Jennifer Zeleny, CPhT
Tim Morley, R.Ph.
Lisa Hulbert, R.Ph.

University of Utah Drug Information Center Staff Present:

Chris Beckwith, PharmD.

Other Individuals Present:

Dan Heincy, Merck
Erica Brumleve, GSK
Mike Swinyard, M.D.
Ann Lingard
Mary Shefchyk, NNI
Ann Gustafson, GSK
Barb Pumphrey, Lilly
Lance Lindberg
Dr. Forman, NNI
Craig Boody, Lilly
Brett Brewer, EMD Serono
Jay Jennings, Sanofi Aventis

Meeting conducted by: Raymond Ward, M.D., Co-Chairperson.

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1. Minutes for September 2008 were reviewed and approved.

2. Legislative Update: Tim Morley addressed the Committee. Michael Hales presented information to the Legislature on September 17th. The PDL is running at about 60% market share for the preferred drug, versus 40% which is overridden. Industry-wide, the market share for preferred drugs runs at about 90% when it is enforced with prior authorization. Utah does not have PA at this time. The Legislature is looking at the performance of the PDL. There are a number of categories on the PDL that are doing very well, particularly those where the only agents in the class are preferred. However, overall it is only about 60%. The information presented will be brought to the P&T Committee so that members can see how the PDL is performing.

3. Insulins – Rapid Acting: Dr. Christina Beckwith addressed the Committee. For the purposes of the P&T Committee, the drugs included in this class are Insulin Asparte, Insulin Glulysine, Insulin Lispro, and Regular Human Insulin. There is some pharmacological diversity in this group. The Insulin Asparte, Glulysine, and Lispro are actually insulin analogs that have a more rapid onset of action than Regular Human Insulin and a shorter duration of action. In general, Regular Human Insulin has an onset within 30-60 minutes and a duration of 3-10 hours. The other three have an onset within 10-30 minutes and have a duration of 3-5 hours. All of the products are available in vials as well as pen or cartridge devices. All of the products are compatible for mixing with NPH insulin or to be given by a continuous infusion pump. In general, in diabetes there are guidelines for treatment from the American Diabetes Association in 2008 for both Type I and Type II diabetes. For gestational diabetes, there are guidelines from The American Diabetes Association as well as the International Workshop Conference on Gestational Diabetes Mellitus from 2007. Neither of those guidelines classify any preference for any of the agents included in this review. For Diabetes Type I and Type II, the key glycemic measure is A1C according to these guidelines, because that is the endpoint that is linked to reduced diabetic complications. For diabetes in pregnancy, the key endpoint that is usually measured is blood glucose, since this is usually a short-term treatment period. As far as methods for this review, the main emphasis was to include randomized controlled clinical trials that evaluated the efficacy of the evaluated agents in at least 20 patients for at least 8 weeks. For Type I and Type II Diabetes, the evaluated trials recorded changes in A1C. For gestational diabetes or pregnant patients, the included trials evaluated either preprandial or postprandial plasma glucose. Only trials that compared the individual agents with each other were included for each indication. The Medline search identified 322 trials. Of these, 49 were included. No meta-analyses were included because they did not evaluate the endpoints of interest. There were no trials included that evaluated the mortality. There have been no long-term trials assessing mortality that have included these agents. Most of the trials that are available compare the other 3 rapid acting agents with regular insulin. There are very few trials comparing Glulysine with Asparte or with Lispro or comparing those agents with each other, so it is difficult to make a judgment on how those compare.

The first key clinical question assessed was how does glycemic control compare between these agents in Type I diabetes. There were 22 included trials. Insulin Asparte, Insulin Lispro, and Insulin Glulysine are at least as effective as Regular Insulin. In summary, Insulin Asparte improves A1C by 0.08-0.4%, Insulin Glulysine improves A1C by 0.11-0.46%, Insulin Lispro improves A1C by 0.1-4% in 10 trials and A1C worsened 0.1-0.3% in 2 trials. With Regular Human Insulin, A1C improved 0.2-4.9% in 14 trials and in 5 trials it worsened 0.2-0.4%. For the comparison of Aparte versus Regular Insulin, in 4 of 6 trials Asparte was better than Regular Insulin. In 2 of 6 trials the two were the same. For Glulysine versus Lispro, one trial found these two products to be similar. There are no other comparative trials between these two agents. Glulysene versus Regular Insulin, the only tria available found that Glulysene was better at controlling A1C. For the comparison of Lispro versus Regular Insulin, 2 of 14 trials found Lispro more effective at controlling A1C, while the other 12 trials found them to be the same.

The second key clinical question, how does glycemic control compare between these agents between Type II diabetes? 9 trials found that Insulin Aspart, Lispro, and Glulysene were at least as effective as Regular Insulin. In comparison between Asparte and Regular Insulin, a single trial found that Asparte was more effective than Regular Insulin. For Glulysene versus Regular Insulin, one of 2

trials found the Glulysene was more effective at controlling A1C, and one of two trials found the two products equally effective. For the comparison of Lispro to Regular Insulin, 2 of 6 trials found Lispro to be more effective, while the other 4 found no difference. Overall with Type II diabetes, Insulin Asparte reduced A1C by 0.4%, Insulin Glulysine by 0.32-0.46%, and Insulin Lispro improves A1C by 0.5-3.2%. Regular Insulin improved A1C by 0.3-0.7% in 7 trials, and worsened A1c by 0.1% in one trial.

The third clinical question, how does glycemic control compare in patients with Gestational Diabetes? Insulin Asparte and Insulin Lispro are at least as effective as Regular Insulin. No comparative trials have assessed Insulin Glulysine in this patient population. For the comparison of Insulin Asparte versus Regular, Asparte was more effective in the single available trial making this comparison. For Lispro versus Regular, one of 3 trials found Lispro to be more effective. The other 2 trials found no difference.

The fourth question, how does glycemic control compare in pregnant patients other than those with Gestational Diabetes? Again, there were no included comparative trials with Insulin Glulysine. Insulin Asparte was more effective than Regular Insulin in the single available trial. Insulin Lispro was more effective than Regular Insulin in one of 4 available clinical trials; the other 3 trials found similar efficacy.

Next, how does glycemic control compare between these agents in children? There are no comparative trials with Glulysine in this population. In one of 2 trials, Insulin Asparte was more effective than Regular Insulin; the other trial found similar efficacy. In all 5 trials, Insulin Lispro and Regular Insulin were similar in efficacy in this population.

How does glycemic control compare between these agents when administered by continuous subcutaneous insulin infusion via the pump? This would be strictly in patients with Type I diabetes. A single compared Insulin Asparte, Insulin Lispro, and Regular Insulin, and found no difference between these three products. Another trial compared Insulin Asparte with Insulin Glulysine, and they had similar efficacy. 5 additional trials compared Insulin Lispro with Regular Insulin, and found that Lispro was more effective in all 5 trials.

Adverse reactions were also assessed in these studies. The next question was how does the safety of these agents compare with each other? Safety of these products is similar. Not all of the clinical trials assessed these endpoints, with the exception of hypoglycemia. As far as discontinuation rates due to adverse events, there was no difference between these agents in the trials that recorded these endpoints.

How do these agents compare in terms of hypoglycemia? Overall, Regular Insulin may be more likely to cause hypoglycemia than Asparte, Glulysine, or Lispro. With Insulin Asparte, 2 of 7 trials found that Regular Insulin was worse than Asparte. The other 5 found no difference. However, this may be due to reduced statistical power to detect differences. Similarly, with Glulysine, 3 of 3 trials found that Glulysine and Regular cause the same frequency of hypoglycemia. A single trial found that Glulysine and Lispro cause the same rate between the two products. For Lispro, 7 of 18 trials found that Regular Insulin was more likely to cause hypoglycemia. The other 11 found no difference. In patients being treated with insulin by continuous subcutaneous infusion, 1 of 7 trials

found that Regular Insulin was worse than Asparte or Lispro. The other 6 found no difference. Looking specifically at nocturnal hypoglycemia, it is difficult to get rates for overall hypoglycemia, because the trials all assess them differently. With Asparte, the rate of nocturnal hypoglycemia is about 4% based on one trial. With Glulysine, there was a rate of 9%. With Regular Insulin the rate varied from 8-14%. With Lispro, the rate was not recorded in this way. Similar to overall hypoglycemia, nocturnal hypoglycemic events were more common with Regular Insulin than the other 3. In 2 of 5 trials comparing Insulin Asparte and Regular Insulin, the Regular Insulin caused more nocturnal hypoglycemic events. For Glulysine 1 of 4 trials found that Regular Insulin was worse than Glulysine. In 4 of 6 studies, Regular Insulin was worse than Lispro for nocturnal hypoglycemia. For patients receiving these products by continuous infusion, Asparte and Lispro have similar rates of nocturnal hypoglycemia, Lispro and Regular have similar rates of nocturnal hypoglycemia. However, one trial found that Regular Insulin was more likely to cause these events than Asparte.

The last key clinical question, how did the safety of these agents compare in special patient populations? In patients with gestational diabetes, these studies did not assess hypoglycemia. There was one study that looked at infant birth weight, and they found that infant birth weight was higher in patients treated with Regular Insulin than in patients treated with Asparte or Lispro. In patients with Type I diabetes outside of the gestational diabetes setting, there were some trials that evaluated hypoglycemia. In one of 2 trials, Regular Insulin caused more hypoglycemia than Lispro; in the other trial Regular Insulin and Asparte caused similar rates of hypoglycemia. In addition, in these patients there were 3 non-randomized trials that were evaluated for these endpoints. In these non-randomized trials, rates of hypoglycemia were similar with Lispro and Regular Insulin. In children, hypoglycemia has been evaluated in 7 studies. In one of those, Regular Insulin was worse and caused more hypoglycemia than Lispro. However, the other 6 trials found no difference. Overall, as far as efficacy, Lispro, Asparte, and Glulycine are at least as effective as Regular Insulin for controlling blood glucose and A1C. It is unclear how the Asparte, Glulysine, and Lispro compare to each other, because there are very few trials that made this comparison. For Glulysine, there are no comparative trials that evaluate the endpoints of interest in either pregnant patients or children. For adverse reactions, hypoglycemia may be more common with Regular Insulin, but there conflicted studies on that. It may be that the studies weren't powered enough to detect these differences.

Dr. Bob Fell from Sanofi Aventis addressed the Committee. Sanofi Aventis has been involved in the discovery of Insulin since 1923. Apidra is a rapid acting analog that used for mealtime insulin. It is approved for the treatment of Type I and Type II diabetes to complement a basal bolus regimen. Based on the data that has been presented and the data that are available, it should be unequivocally clear that there is no difference between the 3 rapid acting analogs. The molecular design of Apidra is unique in that it does not contain zinc. It also contains polysorbate 20, which is a stabilizing agent thought to contribute to stabilizing the drug, and a decreased fibril formation, which is the instability of protein. In stability studies with Apidra for pumps, they were equivalent, but there was a decrease in unexplained hypoglycemia by half. There was also a decrease in occlusions. This was a pilot study, and there is now a larger study with a three-way crossover design between Asparte, Glulysine, and Lispro ongoing. Glulysine has the strongest label in terms of dose flexibility. That is important in terms of a practical and clinical point. Clinically, dose flexibility is important to patients for convenience and so they can dose based on what they ate rather than eat based on how they dosed. Its onset of action is independent of dose and weight or BMI. That has been published in 2 trials,

and additional trials are examining this point. Apidra is the third rapid acting analog in the class, and there are some unique molecular differences. The pediatric trial was presented 3 months ago at the ADA. That manuscript is under review. That trial looked at Glulysine versus Lispro and found no difference. It is a success to show equivalence to the FDA, and this is what has been done in that trial.

Karen Gunning asked if there are studies pending in Gestational Diabetes. There are no studies pending, but there is a registry in place. Not too many companies will actively seek a pregnancy label with the FDA. Right now Apidra has a few case reports, but that's all.

Dr. Mike Swinyard addressed the Committee. Dr. Swinyard is a full-time pediatric endocrinologist. About 500 patients with Type I Diabetes are managed in his practice. He does not see patients with Gestational Diabetes or Type II Diabetes. He sees patients from the 5-state region, and holds clinics in Missoula and Boise on a regular basis. Patients in his South Jordan practice are seen from West Yellowstone to Las Vegas and between Elko and Casper, WY. Only 10% of his patients are Medicaid. Dr. Swinyard has Type I Diabetes, and has been on insulin for most of his life. He has no conflicts of interest, does not own stock in any of the companies represented at the meeting, is not on any speakers' bureaus, and does not receive payment for any insulins that he prescribes. Post prandial glucose is a very important issue among children and adolescents. Being able to give insulin post-meal to 3-year old children is very important, as they do not always eat the correct number of carbs to match their pre-prandial insulin dose. It is also important for adolescents, as they try to time when they eat with meeting and eating with friends. Timing is as important as carb counting in post prandial glucose control. His experience with the 3 analongs has been largely a forced experience with a large group of patients who are under Select Health plans. That large insurer recently decided that they would only offer Novolog as their treatment option. At least 40-50 patient had to change to that option, despite the slower onset and longer duration of Novolog. These were patients who were on intensive therapy of injections, or insulin pumps. They noted that if they had to have reasonable post prandial glucose control, there was a significant difference in how long they had to wait with Novolog versus Humalog. He only has a limited experience with Apidra, so he cannot comment on Apidra at this time. He has had this experience with Novolog versus Humalog, and that is what he would like to comment on at this time. The Committee should consider having at least 2 options of Analog Insulins at this time. Pharmacodynamically, there are differences in how these different insulins work, even though the pharmacokinetic data may support equivalence with serum levels after injection or infusion. Also, Medicaid should consider using pens or pen cartridges. Pen devices are a good idea in design, but it is difficult to have pediatric patients hold still for 7-10 seconds while the pen device infuses. In pediatric patients, it is difficult to use up a 10ml vial in a month. Pen cartridges offer the option of less waste and lower cost to patients and health plans.

The Committee asked why there are differences in A1C drops between Regular Insulins versus Analogs. Could this be due to socioeconomic differences? Is it possible that the patients using Regular Insulin have higher drops due to higher baseline A1C? It is true that it is more difficult to drop one point from, say, 8 to 7 than from 12 to 11. Socioeconomically, there are patients who are highly motivated patients. People with diabetes can take the tools that they have and make the best of it if they are given good education. If there were to be no access to Insulin Analogs today, it could work. But he would have to be much more careful in what he ate, when he ate, and the possibility of

a late post-prandial hypoglycemic effect. As we enter the era of continuous blood glucose monitoring, differences between the 3 analogs will be better teased out. It is nice to be able to have a variety of different tools.

The Committee asked if there were problems with converting all of his patients to Novolog when the commercial health plan required it. Were there enough educators? Were there any problems? Dr. Swinyard had his patient talk to IHC. Due to the pressure of the clients, IHC now covers Humalog under a DME benefit. The Committee asked why it is necessary to stay on Humalog. It is necessary because of the post-prandial onset and slower duration, which is poor with Novolog. With Humalog, patients can give a correction dose for hyperglycemia without having a hypoglycemia due to overlap with their next mealtime dose.

Dr. Bob Forman with Novo Nordisk addressed the Committee. He is an endocrinologist practicing in New Haven, CT for 31 years. He now works for Novo Nordisk as a Medical Director. When drug companies do studies, they do studies comparing their drug to the gold standard, which is Regular Insulin. This makes the job of the Committee very hard, because the analogs are not directly compared. Regular Insulin does contain zinc. The study that was referenced by Dr. Fell was an in-house unpublished Sanofi study that showed occlusion. There are published studies by independent investigators with support from PhRMA that show less occlusion with Novolog in pumps. The differences that are seen are probably minor, in the sense that they affect issues other than activity. In his practice, he did do pediatrics and adult. There was very little delay of onset seen with Novlog. All insulin analogs do begin to work within 10-15 minutes and last 3-5 hours. The TMax of Novolog is very well-defined within a 10 minute window of 40-50 minutes. The other two analogs are from 30-90 minutes with Lispro, and from 34-91 minutes for Glulysine. Certainly, hypoglycemia in most studies, as compared with Regular Insulin, has been less with the analogs. Asparte insulin is very stable, especially in Salt Lake City where it gets up to 97 degrees. The other two Analog Insulins are less heat stable. Novolog has an indication down to age 2, it is a class B in pregnancy, and has even been used in geriatrics up to 91 years old in some studies. Patients who take analog insulin are more compliant. Because it is a more predictable dose, they don't worry about getting hypoglycemic, nor do they get hyperglycemic. The small doses that the pediatrician was alluding to can be alleviated by the Junior Pen device that can give doses in half-unit increments. The pen can also reduce waste with small doses of insulin. Novolog has been shown in some studies to be more effective in the pump. The Swan-Zimmer study out of Yale showed that less Asparte was needed than Lispro to control blood sugar. Non-inferiority studies have shown that A1C is the same. In general, this is a stable insulin with good indications, class B pregnancy label, and few occlusions. Novo Nordisk also has a full portfolio with a 70/30 mixture and basal Levimir, and it is good for diabetes educators to be able to use the same devices across the board with their patients.

Karen Gunning asked Dr. Beckwith if there were any switching trials available. There were no switching trials that addressed the endpoints of interest.

Dr. Beckwith stated that Karen had asked about available trials discussing the various different devices that are available. There was only one trial that assessed patient satisfaction with the Novo Nordisk products, comparing the Insulin Pens with the vials and syringes. They found that patients tended to prefer pens, and were more likely to recommend those devices to other people. There were no other studies comparing the different devices made by different companies with one another.

Medicaid currently requires a PA for Insulin Pens. At this point, it is only available for the legally blind who cannot use other adaptive devices.

Jerome stated that diabetes is clearly on the rise. Compliance is clearly an issue for diabetics. Costs for the program could rise if the Committee decision were to effect compliance.

Karen stated that the presenters spoke primarily about Type I diabetes. There are probably more Type II diabetics on the Medicaid program. They have very different issues from Type I diabetics. Does Medicaid have any sense of how many diabetics are Type I versus Type II? Medicaid only has age ranges available for patients receiving insulin.

Koby stated that he does a lot of work with Diabetes Camp and he does see many kids on a wide range of these products. People do respond to them differently. At camp, they are given free insulin from the manufacturers. Often, the kids are given all 3 of the analogs at check-in. They will talk about the differences between them. The reality is that there are differences between them. If one child decides to dose on Apirdra, they can crash because it is different and they are not used to it. He is concerned that pharmacists may either wait to dispense a different product if a patient presents with a prescription for a non-preferred product, or may make the patient wait over a weekend before dispensing. From his standpoint, this is not a good category for a preferred product, because the patient may be possibly put at risk. There are not systems in place with Medicaid to prevent this type of situation, and it cannot be guaranteed that the pharmacist will do any of those things.

Tim Morley stated that due to the work schedule imposed on Medicaid, Medicaid will back up a pharmacist that has a difficult decision to make on a Friday. Medicaid will need to support the pharmacist in making the best decision that he can. Once Medicaid speaks with the pharmacist on Monday, the policy is that Medicaid will need to back him up. The pharmacist needs to make the best decision with the resources possible. Getting the word out is Medicaid's challenge. Medicaid needs to allay the concerns of pharmacists needing to make difficult decisions on Fridays.

Dr. Ward stated that based on the evidence presented by Dr. Beckwith, this is the best evidence presented that there is no clear difference between any of the agents.

The Committee stated that the presentation of Dr. Swinyard suggested that there are differences in the Select Health patients that were switched. There is no reason to think that the relatively resource-less population of Medicaid wouldn't be adversely effected by being forced to switch.

Koby stated that Select Health had a huge program to assist patients with switching insulins, with educator and protocols for switching. Would Medicaid have the resources to have something like that? Or could a patient ultimately end up in the hospital due to the way that the switch was handled?

Tim Morley stated that Koby had a good point earlier when he stated that people do not respond to these insulins consistently. Because of the lack of consistency, does it make sense to have a standard approach to the problem, or should Medicaid just leave it open and wing it?

Dr. Ward stated that most commercial insurers do have a standard approach and require a preferred

product. Karen Gunning added that Medicaid also have a very easy override system compared to commercial insurers. The physicians for the pediatric endocrinology patients, who really cannot switch, will definitely back up medical necessity in their records. Karen understood Koby's concerns. As much as she dislikes the override system for the PDL, it actually works really well for this situation.

Lisa Hulbert asked if an educational article for providers would be beneficial, particularly an article dealing with this category. Koby felt that this was helpful. The Committee felt that the pediatric endocrinologists should be easy to identify and notify.

Koby stated that as a pharmacist he has issues with the PDL. For the last year he has asked to have the cumulative monthly limits removed from the PPI's. To date this still has not happened. Karen Gunning stated that this is actually a DUR Board decision and not a P&T Committee issue.

Dr. Beckwith stated that there are only four agents under consideration for this meeting, Regular Insulin and the Analogs.

Dr. Ward stated that no one would interchange Regular Insulin with an Analog and expect them to work the same. Karen added that there are actually two decisions that needed to be made: One decision with regard to the Regular Insulins and a separate decision with regards to the Analogs.

Jerome Wohleb made a motion for there to be at least one preferred Regular Insulin to be considered by Medicaid. Karen Gunning seconded the motion. The motion passed with votes by Kort Delost, Dr. Harris, Dr. Weeks, Karen Gunning, Duane Parke, Dr. Ward, and Jerome Wohleb. Koby Taylor voted against the motion.

Dr. Harris made a second motion that there be at least two Analog agents on the PDL. Karen Gunning added that the lack of evidence in gestational diabetes and pediatric patients in Glulysine is concerning, although there are some in press. Duane Parke seconded the motion. The motion passed with votes by Kort Delost, Dr. Harris, Dr. Weeks, Karen Gunning, Duane Parke, Dr. Ward, and Jerome Wohleb. Koby Taylor voted against the motion.

Next Meeting Set for Thursday, October 16, 2008
Meeting Adjourned.

Minutes prepared by Jennifer Zeleny